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BIOMIMETIC DRUG DELIVERY SYSTEMS: HARNESSING NATURE'S INSPIRATION

Niranjan Babu Mudduluru[*1], Santhivaradhan Chinni[2], Yogasree Rajendra[3]

[1]Department of Pharmacognosy, Seven Hills College of Pharmacy, Tirupati, A.P., India
[2]Department of Pharmacology, Seven Hills College of Pharmacy, Tirupati, A.P., India
[3]Department of Pharmacology, Seven Hills College of Pharmacy, Tirupati, A.P., India

Corresponding Author
Dr. M. Niranjan Babu
Professor Department of Pharmacognosy Seven Hills College of Pharmacy, Tirupati, A.P., India – 517561, Contact: 7702484513, Email: principal.cq@jntua.ac.in

Abstract:

Modern drug delivery systems are increasingly focused on targeted medication delivery. This includes improving drug loading capacity in carriers, enhancing cellular uptake, and achieving sustained release within target cells. This review explores six categories of therapeutic drug carriers: biomimetic hydrogels, biomimetic micelles, biomimetic liposomes, biomimetic dendrimers, biomimetic polymeric carriers, and biomimetic nanostructures. Biomimetic production and surface modification techniques are utilized to mimic natural cell accumulation processes. These biomimetic strategies are shown to enhance drug efficiency in targeted drug delivery systems. The study suggests that biomimetic nanocomposite drug carriers have the potential to significantly improve medication effectiveness in specific delivery systems.

Keywords: Biomimetic, targeted drug delivery, Drug carriers.

Introduction:

The term "biomimetic" was first coined by Otto Schmidt in 1957. Schmidt described biomimetics as a viewpoint rather than a specific subject matter, emphasizing its application of biological science theory and technology to solve technological challenges. Synonyms for biomimetics include "biomimesis," "biomimicry," "bionics," "biognosis," and "biologically inspired design," with "biomimetics" being the most widely recognized and practical term [1].

One promising application of biomimetics is in the treatment of terminal illnesses like cancer, where it addresses critical issues in pharmaceutics and medicine. Recent scientific efforts have focused on gaining a precise understanding of biological systems and processes. This includes studying macromolecular structures, such as proteins, and their functions at cellular and subcellular levels. Insights from these studies inspire and inform the development of biomedical applications through biomimetic approaches[2].

Current research in drug delivery systems is primarily centered on targeted drug delivery, allowing medications to enter specific cell cytoplasms without harming healthy tissues or organs. The advent of nanotechnology has enabled the encapsulation of drugs in nanocarriers. Significant advancements have been made in overcoming challenges related to insoluble medications, biodegradable therapeutic agents, and drugs that pose high risks to biological systems. The small size of nanoparticles facilitates intercellular diffusion, although achieving targeted release into specific cells remains a challenge [3].

Since 1986, a significant challenge in nanoparticle technology has been extending their circulation time in bodily fluids to enhance drug delivery into tumor cells through the permeability and retention (EPR) effect. Nanoparticles are typically recognized and eliminated by the reticuloendothelial system (RES) as foreign bodies, often binding plasma proteins like immunoglobulin G (IgG) to their surface. To mitigate this, various hydrophilic polymers have been used to coat nanoparticles covertly, thereby improving their EPR effect and evading immune recognition. Polyethylene glycol (PEGylation) has been a popular choice for surface coating nanoparticles over the past thirty years. However, PEGylated nanoparticles often face challenges such as poor cellular uptake and drug degradation in lysosomes due to undesired interactions with target cells (known as the PEG dilemma). Functional ligands such as proteins, vitamins, peptides, antibodies, and aptamers can be added to the surface of PEGylated nanoparticles using biomimetic approaches to overcome these barriers. Selection of these ligands considers the overexpression of specific receptors on tumor cells, facilitating receptor-mediated attachment.

Biomimetics in advanced drug delivery systems focus on surface modifications using amino acids, saccharides, and lipids to impart inherent biomimetic capabilities to drug carriers. By mimicking natural cell structures for cellular internalization, attention is paid to the composition, size, and shape of drug carriers. Functionalizing the surface of nanocarriers with biological ligands or moieties resembling external cell membranes enables targeted drug delivery within specific cells. Biomimetic drug carriers fall into two main categories based on their basic materials: synthetic nanoparticles designed to mimic biological materials and existing biological entities like inactivated viral and bacterial vectors, which are safer for in vivo therapeutic applications[4].

Over the past three decades, controlling drug release rates and harnessing PEG's stealth properties to evade immune detection have been primary concerns. Current research focuses on biomimetic processes that replicate cellular microenvironments, engineer drug carrier surfaces, and draw inspiration from signal pathways crucial for intracellular communication within the body. Scientists aim to enhance drug carriers' circulation half-lives, suppress immunological responses, minimize toxicity to healthy cells, and achieve sustained drug release through effective cellular internalization in target cells [5].

Biomimetic hydrogels: Hydrogels are a class of hydrophilic polymeric materials, either synthetic or natural, capable of absorbing large volumes of water or biological fluids, thereby remaining in solution in aqueous environments. This property is achieved through physical or

chemical cross-linking of polymer chains. These biomaterials offer customizable porosity, biocompatibility, softness, and flexibility as key attributes. The gel formation conditions are mild enough to closely mimic those found in natural biological tissues and cells. Modifications to the hydrogel matrix can impart unique characteristics that enable rapid and reversible responses to various chemical and physical stimuli, such as changes in pH, temperature, and ionic strength, making them suitable for long-term, sustained drug release. This capability allows them to effectively transport biomolecules like protein and peptide therapeutics [6].

Biomimetic hydrogels have evolved by incorporating biological recognition sites that mimic cellular activities and synchronize responses to external stimuli. Inert polymer chains of hydrogels can be customized with specific biological components to facilitate targeted in vivo drug delivery systems. Moreover, by integrating biological cues such as proteins, growth factors, and peptides into hydrogel matrices in a spatial and temporal manner, it becomes feasible to replicate the cellular microenvironment. This approach creates a unique, controlled drug delivery system capable of tissue regeneration [7].

Biomimetic micelles: In chemistry, the term "micelle" describes a structure in aqueous solutions consisting of a single hydrophobic core surrounded by a hydrophilic shell. These structures are employed in drug delivery systems, particularly for treating diseases such as cancer.

Polymeric micelles are a prominent colloidal delivery technology due to their excellent capacity for drug modification. These nanoscale spheres are typically formed by self-assembly of amphiphilic di- or tri-block copolymers in an aqueous environment. The hydrophilic shell interacts with the biological environment, providing stealth properties, while the hydrophobic core encapsulates and solubilizes hydrophobic substances like proteins or DNA. By altering the chemical structure of block copolymers in micelles, one can design or modify pathophysiology specific drug release mechanisms and the physicochemical properties of the encapsulated drug. Changes in the core's chemical structure can enhance drug encapsulation, stabilize micelles, and control drug release rates.

Biomimetic micelles can be created by incorporating biological moieties or biomimetic block copolymers into the self-assembly of innovative biomimetic amphiphiles in micellar structures. For instance, Xu et al. (2005) developed biomimetic amphiphiles using PEO and cholesterol (Chol), mimicking the cholesterol component of cell membranes that regulate membrane fluidity. These Chol-PEO micelles efficiently encapsulated hydrophobic anticancer drug doxorubicin (ADR), demonstrating effective drug loading and sustained release in vitro. Similar approaches were explored using cholesterol-capped poly (2-methacryloyloxyethyl phosphorylcholine) (CMPC) micelles, which provided a biocompatible shell in contact with human tissues [8].

Protein polymers have also been utilized as copolymer blocks in biomimetic micelles for drug delivery systems. Sallach et al. (2006) utilized reversible helix-to-sheet protein folding transitions as a model. They designed protein triblock copolymers from elastin-mimetic

peptide sequences, where one hydrophilic block formed the core and two hydrophobic blocks constituted the shell of these biomimetic micelles. This structural feature allowed rapid response to environmental stimuli such as heat, influencing micellar size and compression.

Biomimetic liposomes: Liposomes are spherical vesicles composed of phospholipids arranged in a double-layered or bilayered structure. They are attractive for drug delivery due to their similarity to animal or human cell membranes. Liposomes self-assemble in aqueous solutions, utilizing cholesterol and naturally occurring phospholipids. Their structure includes an aqueous center surrounded by concentric phospholipid bilayers, imparting both hydrophilic and hydrophobic properties. Liposomes are biocompatible, biodegradable, and non-toxic, capable of carrying hydrophilic drugs in their interior aqueous compartment and hydrophobic drugs within the phospholipid bilayer. They vary in lipid composition, surface charge, size, and manufacturing process, categorized as unilamellar vesicles (UV) or multilamellar vesicles (MLV) based on size and bilayer number [9].
Biomimetic liposomes can mimic biological cell functions, delivering drugs or biomolecules intracellularly when targeted with specific ligands or moieties. They possess the capability to release their cargo actively or passively at a controlled rate in response to stimuli within the cellular microenvironment.

In 2001, Westhaus and Messersmith developed thermal-responsive liposomes capable of encapsulating CaCl2 and releasing it at body temperature. These biomimetic liposomes were inspired by the rapid gelation of Ca+2 with polysaccharides like protein and alginate. CaCl2-loaded liposomes have potential applications as biomaterials for tissue regeneration or as injectable medications for in situ use. Additionally, Sakai et al. created PEG-coated liposomes containing entrapped hemoglobin (Hb-vesicles), enabling artificial oxygen transfer akin to red blood cells. In vivo experiments demonstrated moderate metabolism in the reticuloendothelial system following bolus infusion of HbVs, suggesting promising applications for treating related blood disorders [10].

Biomimetic dendrimers: Dendrimers are synthetic polymers that resemble tree-like structures, designed and customized to function as drug carriers in advanced drug delivery systems. These compact, spherical macromolecules have highly branched, three-dimensional architectures with internal repeating units, or generations, radiating from a central core. They exhibit a defined shape, size, molecular weight, and uniformity of functional groups (terminal groups) on their surface, making them ideal candidates for drug delivery systems. Drugs can be encapsulated within the dendritic structure or attached to the surface through covalent or electrostatic interactions with these functional groups. Dendrimers enhance the bioavailability, biocompatibility, and water solubility of drug molecules. However, considerations regarding their toxicity include surface charge, composition, and number of generations, with cationic dendrimers generally showing higher toxicity due to potential interactions triggering apoptosis in cell membranes and organelles.

Biomimetic drug carriers can be created by attaching specific ligands to the reactive terminal groups on dendrimers' surfaces, enabling targeted drug delivery. Moreover, these

macromolecules can mimic natural proteins and other materials due to their unique monodispersity and self-assembly capabilities.

In 2004, Paleos et al. modified diaminobutane poly(propylene imine) (DAB) dendrimers by introducing guanidinium ligands and PEG chains on the external surface. This modification improved stability in physiological media and reduced adverse effects by providing a stealth cover and targeting feature via receptors. In vitro studies evaluated the solubility and release profiles of encapsulated pyrene and betamethasone valerate in these multifunctional dendrimers. Huang et al. utilized room temperature ring-opening polymerization (ROP) to synthesize multi-armed dendrimers from poly(amidoamine) (PAMAM) by coupling β-benzyl-L-glutamate N-carboxyanhydride (BLG-NCA) with initial amine-ended groups. This approach yielded biomimetic dendrimers with a structure resembling proteins, capable of forming stable globular nanoparticles as carriers for drugs or genes when dispersed in water.

Biomimetic polymeric carriers: Polymeric carriers offer several advantages for drug delivery applications, including their ability to be produced at the nanoscale, high drug loading capacity, controlled release characteristics, and surface modification capabilities due to active functional groups. Biomimetic polymers represent a new class of biomaterial carriers designed to mimic cellular interactions such as endocytosis, cytokine signaling, and cell adhesion. These polymers enable the transport of drugs across cell barriers into targeted diseased cells through physiologically active components. An ideal biomimetic polymeric carrier should elicit specific cellular responses necessary to reach its target while minimizing nonspecific interactions on cell surfaces.

Key challenges in optimizing biomimetic polymeric carriers include determining specific drug release mechanisms and diffusion models through stoichiometry optimization in polymerization techniques and biomimetic structure design.

In 2006, Zhang et al. developed a dual-functional biopolymeric material capable of conjugating with biological ligands, composed of zwitterionic poly (carboxybetaine methacrylate) (polyCBMA) grafted onto a gold surface. This material effectively resisted nonspecific protein adsorption by immobilizing specific proteins, such as anti-human chorionic gonadotropin, thus demonstrating its utility in drug delivery systems and medical diagnostics.

Duncan synthesized HPMA (N-(2-hydroxypropyl)methacrylamide) copolymer conjugates in 2007, incorporating the aromatase inhibitor aminogluthimide and the chemotherapeutic drug DOX. These conjugates were designed for specific molecular mass selection to target malignancies through endocytosis internalization, marking them as the first biodegradable polymer-drug conjugates studied in phase I/II clinical trials.

Ho et al. developed a biomimetic endosomalytic polymer by grafting PP-75 (L-phenylalanine stoichiometric grafting) onto pendant carboxylic acids of a polyamide (poly(L-lysine isophthalamide)). PP-75's small size facilitated penetration into tumor spheroids and intracellular drug release without harming other live cells, while its hydrodynamic size variation depended on lower pH conditions. These properties highlight PP-75's potential for further clinical investigation in vivo applications.

CONCLUSION:

Recent advancements in biomimetic drug carriers have significantly enhanced targeted medication delivery efficiency. These innovations have led to improved drug loading capacities, cellular uptake of drug carriers, and sustained release within target cells.

Biomimetic hydrogels, designed to mimic cellular microenvironments akin to extracellular matrices, have proven highly effective for localized drug delivery. Physicochemical enhancements in biomimetic micellar carriers have stabilized their structures, facilitating sustained drug release and protecting loaded medications until they reach their intended targets. Similarly, biomimetic modifications to liposome surfaces and fabrication techniques have enhanced the ability of therapeutic liposomes to target drug delivery by improving the enhanced permeability and retention (EPR) effect.

Biomimetic PAMAM dendrimers have facilitated intercellular drug uptake for targeted drug delivery, while biomimetic polymeric carriers have streamlined endocytosis for intracellular drug release. Other biomimetic nanostructures, employing both organic and inorganic materials (nanocomposite drug carriers), have also shown significant improvements in pharmaceutical loading, cellular absorption, and drug release profiles.

Although much of the research on biomimetic drug delivery systems has been conducted in vitro, rapid advancements suggest promising prospects for successful in vivo applications in treating various diseases.

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